## REMARKS

In view of the following remarks, the Examiner is requested to reconsider and allow Claims 1 – 28, the only claims pending and under examination in this application.

Claims 1 – 28 are pending in this application. Claims 1 – 28 have been rejected. Claims 1, 24 and 28 have been amended to correct minor grammatical errors. Accordingly, these amendments add no new matter and their entry is respectfully requested.

As an initial matter, the Applicants thank the Examiner for withdrawing the rejection of Claims 1 – 5 and 19 – 27 under 35 U.S.C. §112, second paragraph; for withdrawing the rejection of Claims 1 – 18 and 24 – 28 under 35 U.S.C. §103(a), as allegedly being unpatentable over Petrus (USPN 6,399,093) in view of Biedermann, et al. (USPN 5,980,921); and for withdrawing the rejection of Claims 19 – 23 under 35 U.S.C. §103(a) as allegedly being unpatentable over Petrus in view of Biedermann, et al. and Shudo, et al. (USPN 6,761,900).

### CLAIM REJECTIONS – 35 U.S.C. §103

Claims 1 – 18 and 24 – 28 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Petrus (USPN 6,399,093) in view of Edwards (USPN 5,989,559) and Biedermann, et al. (USPN 5,980,921).

The present invention is directed to ameliorating a symptom associated with pressure applied to the median nerve of the carpel tunnel syndrome. Specifically, the claimed invention is directed to the application of an effective amount of a topical NSAID formulation to a palmer dermal surface proximal to the carpal tunnel. An element of the rejected claims, therefore, includes the application of a topical NSAID formulation to a palmer dermal surface proximal to the carpal tunnel for at least ameliorating a symptom associated with pressure applied to the median nerve of carpal tunnel.

The Examiner contends that the cited art renders the presently claimed invention obvious because the prior art: 1) discloses the use of compositions for the treatment of musculoskeletal disorders (of which the Examiner contends CTS is a member); 2) generally discloses compositions that contain the same ingredients and active agents as those of the claimed invention; and 3) discloses the use of compositions proximal to a site of pain.

However, a *prima facie* case of obviousness has not been established with respect to the presently claimed invention because the combined teaching of Petrus, Edwards and Biedermann fails to teach or suggest all the limitations of the claimed invention.

As set forth above, an element of the claimed invention is the application of a topical NSAID formulation to a palmer dermal surface proximal to the carpal tunnel for at least ameliorating a symptom associated with pressure applied to the median nerve of the carpal tunnel.

The Examiner cites Petrus for teaching a treatment of musculoskeletal disorders by the topical application of an NSAID. The Examiner asserts that musculoskeletal disorders are a genus that encompass carpal tunnel syndrome.

However, carpal tunnel syndrome is not a species of musculoskeletal disorders. As stated above, carpal tunnel syndrome is a condition caused by a disturbance of median nerve function in the wrist as the nerve passes through the carpal tunnel. Hence, contrary to the Examiner's contention, CTS is not a musculoskeletal disorder, where the symptoms originate from the soft tissues, muscle, tendon, and ligament, or bone. Rather CTS is a neurological disorder and by definition is an entrapment neuropathy, where the symptoms originate from peripheral nerve. See Exhibit A (www.ninds.nih.gov/disorders/carpal_tunnel/detail_carpal_tunnel.htm). See also Exhibit B: MacDermid & Doherty, "Clinical and electrodiagnostic testing of carpal tunnel syndrome: a narrative review,"*J Orthop Sports Phys Ther.* 2004 Oct;34(10):565-88. Importantly, the diagnosis and generalized medical care for neuropathies are quite distinct than that of musculoskeletal disorders.

Because Petrus is not directed to the treatment of neurological disorders generally, let alone to the specific treatment of carpal tunnel syndrome, Petrus does not teach or suggest ameliorating a

symptom associated with pressure applied to the median nerve of carpal tunnel; a limitation recited in the rejected claims.

As Edwards was cited to "point out that it is well known in the prior art to apply a topical or transdermal pharmaceutical formulation at the site proximal to the source of pain," and Biedermann was cited "to show that diclofenac and indomethacin are known in the art as acetic acid derivatives," they fail to remedy the deficiencies of Petrus, i.e., ameliorating a symptom associated with pressure applied to and inflammation of the median nerve of carpal tunnel, caused by an entrapment neuropathy. Accordingly, the combination of Petrus, Edwards and Biedermann fails to teach or suggest every element of the rejected claims and for at least this reason the Applicants respectfully request the rejection be withdrawn.

Additionally, the combined teaching of Petrus, Edwards and Biedermann fails to provide a reasonable expectation of success in the Applicants' claimed invention. As explained in the Declaration of Dr. Larry Caldwell filed in conjunction with the Applicants' April 26, 2004 response, a reasonable expectation of success cannot be expected by modifying the invention of Petrus in view of Edwards and Biedermann because in so doing one would not only have to change the condition to be treated, i.e., from a muskuloskeletal disorder to a neurological disorder, but also the pathway of administration.

The Examiner, however, disregards the filed declaration by asserting that the §1.132 declaration is not persuasive because neither the premises nor the conclusions therein are supported by an evidence of fact. However, according to the MPEP §716.01 (c):

> "Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue."

Dr. Caldwell is a reasonably skilled practitioner in the field. His declaration is not submitted as to the ultimate legal conclusion at issue, i.e., obviousness. Rather it is submitted to establish what a reasonably skilled practitioner in the art knows. In his knowledgeable opinion, he is asserting the facts that:

(a) it is well known in the art that just because an active agent is administered orally to treat a medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition; and

(b) it is well known in the art that just because an active agent is administered topically to treat one condition does not mean that it can be effective when topically administered to treat other conditions, **especially when they differ in underlying tissue involvement, i.e. nerve versus musculoskeletal.**

Accordingly, based on these facts, just because a topically administered NSAID is effective at treating one condition does not mean it will necessarily be effective at treating a different condition, especially if the administration sites and target tissues differ in biology.

As stated above, Petrus is not directed to treating CTS, but rather to treating musculoskeletal disorders. Unlike musculoskeletal disorders, CTS originates deep within the nerve, whose symptoms are caused by pressure applied to and inflammation of a peripheral nerve . For an active NSAID agent to be effective, it must penetrate deeply through the carpal tunnel in order to reach the target site. Accordingly, the NSAID agent must cross the barriers of the carpal tunnel and penetrate the median nerve to be effective for relieving pressure and inflammation and thus alleviating the symptoms of CTS.

Because Petrus is not directed to the treatment of neurological disorders or to the treatment of neuropathies, such as the entrapment neuropathy of CTS, especially via the application of an NSAID in areas with significantly high barriers to penetration, such as the palmar dermal area proximal to the median nerve of the carpal tunnel, prior to the Applicants' work there was no certainty that a sufficient amount of an active NSAID agent would be able to penetrate deeply enough to be effective in treating CTS/median nerve pressure and inflammation.

As Edwards is directed solely to the use of a banana peel extract composition and not to the application of an NSAID and Biedermann was cited solely "to show that diclofenac and indomethacin

are known in the art as acetic acid derivatives," there is no reasonable expectation of success in the Applicants' claimed invention provided by the combined teaching of Petrus, Edwards and Biedermann.

Accordingly, a reasonable expectation of success in the Applicants' claimed invention has not been provided by the cited art because, outside of the Applicants' teachings, one of skill in the art upon reviewing Petrus, Edwards and Biedermann would not expect 1) that the formulations of Petrus would be beneficial for treating CTS, 2) that the topical administration of such a formulation would be able to penetrate the barriers of the carpal tunnel (e.g., the flexor retinaculum sheath) and contact the median nerve, and 3) that the formulation would be successful in treating median nerve pain and/or CTS.

Therefore, as explained above, a *prima facie* case of obviousness has not been established with respect to the presently claimed invention because the cited art does not teach or suggest every limitation of the claimed invention and a likelihood of success has not been provided. The Applicants therefore respectfully request the Examiner to reconsider and withdraw the 35 U.S.C. §103 obviousness rejection and allow the pending claims.

Claims 19 – 23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Petrus (USPN 6,399,093) in view of Edwards (USPN 5,989,559), Biedermann, et al. (USPN 5,980,921), and Shudo, et al. (USPN 6,761,900).

Claim 19, and the claims dependent therefrom, are directed to kits that include a topical NSAID formulation and instructions for using the NSAID formulation in accordance with a method according to Claim 1. As demonstrated above, Petrus, Edwards and Biedermann do not teach or suggest every limitation of Claim 1 or provide a reasonable expectation of success in the claimed invention of Claim 1.

As Shudo was cited for its disclosure of kits containing topical patch formulations and instructions, it fails to remedy the defects of Petrus, Edwards and Biedermann, and therefore a *prima facie* case of obviousness has not been established with respect to Claims 19 – 23. Accordingly, the Applicants respectfully request the Examiner reconsider and withdraw this rejection.

## CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CALD-005.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 1/5/06 By: _____
James S. Nolan
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Date: 1.5.06 By: _____
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Enclosure:

- Exhibit A (www.ninds.nih.gov/disorders/carpal_tunnel/detail_carpal_tunnel.htm)
- Exhibit B: MacDermid & Doherty, "Clinical and electrodiagnostic testing of carpal tunnel syndrome: a narrative review," *J Orthop Sports Phys Ther.* 2004 Oct;34(10):565-88.

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